

FOOD AND DRUG ADMINISTRATION
Center for Tobacco Products (CTP)

Tobacco Product Constituents Subcommittee
of the
Tobacco Products Scientific Advisory Committee (TPSAC)

Hilton Washington DC North/Gaithersburg, Gaithersburg, Maryland

July 7, 2010

These summary minutes for July 7, 2010 meeting of the Tobacco Product Constituents Subcommittee of the Tobacco Products Scientific Advisory Committee of the Food and Drug Administration were approved on ____8/17/10____.

I certify that I attended the July 7, 2010 meeting of the Tobacco Product Constituents Subcommittee of the Tobacco Products Scientific Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

____---S---____
Karen M. Templeton-Somers, Ph.D.
Acting Designated Federal Official

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Dorothy Hatsukami, Ph.D.
Chair, Tobacco Product Constituents Subcommittee

The Tobacco Product Constituents Subcommittee of the Tobacco Products Scientific Advisory Committee of the Food and Drug Administration, Center for Tobacco Products met on July 7, 2010 at the Hilton Washington DC North/Gaithersburg, Gaithersburg, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the submissions from the public. The meeting was called to order by Dorothy Hatsukami, Ph.D. (Subcommittee Chair); the conflict of interest statement was read into the record by Karen M. Templeton-Somers, Ph.D. (Acting Designated Federal Official). There were approximately 60 persons in attendance. There were no speakers for the Open Public Hearing session.

Proposed Agenda: The subcommittee will continue discussions, as needed, from the June 8-9 meeting of this subcommittee. The subcommittee will then receive presentations and discuss the analytic methods and ancillary and normalization standards applicable to the measurement and reporting of harmful or potentially harmful constituents in tobacco products, including smoke constituents. The subcommittee will finalize its proposed list of harmful or potentially harmful constituents, the rationale for inclusion of each substance, validated methods for measuring the constituents and the ancillary and normalization standards for the identified constituents for presentation at a future meeting of the Tobacco Products Scientific Advisory Committee.

Attendance:

Tobacco Products Scientific Advisory Committee Members Present (Voting):

TPSAC Members (*voting*): Dorothy K. Hatsukami, Ph.D. (Chair)

TPSAC Members (*non-voting Industry Representatives*):

Luby Arnold Hamm, Jr. (Representative of the interests of tobacco growers); Jonathan Daniel Heck, Ph.D., DABT (Representative of the tobacco manufacturing industry); John H. Lauterbach, Ph.D., DABT (Representative for the interest of small business tobacco manufacturing industry)

Consultants (*non-voting*): David Burns, M.D., Mirjana Djordjevic, Ph.D., William A. Farone, Ph.D., Stephen S. Hecht, Ph.D., Jennifer Jinot, Richard O'Connor, Ph.D., Clifford Watson, Ph.D.

FDA Participants at the table (*non-voting*): David L. Ashley, Ph.D., Corinne G. Husten, M.D., M.P.H., Glen D. Jones, Ph.D.

Designated Federal Official (*Acting*): Karen M. Templeton-Somers, Ph.D.

The Agenda proceeded as follows:

July 7, 2010

Call to Order	Dorothy Hatsukami, Ph.D. Chair Tobacco Product Constituents Subcommittee
Conflict of Interest Statement	Karen M. Templeton-Somers, Ph.D. Acting Designated Federal Official, FDA
Introduction of Subcommittee Participants	
Charge to the Group: Harmful and Potentially Harmful Tobacco Product Constituents	Corinne Husten, M.D., M.P.H. CTP
Tobacco Constituents: Discussion of Abuse Liability	Allison C. Hoffman, Ph.D. CTP
Subcommittee discussion of constituents associated with abuse liability	
Subcommittee discussion of the list of harmful or potentially harmful constituents in tobacco products, including smoke constituents	
Subcommittee discussion of analytic methods and ancillary standards	
Open Public Hearing	
Subcommittee discussion of the <i>Questions to the Subcommittee</i>	
Adjourn	

Questions to the Subcommittee:

1. What criteria do you recommend to TPSAC for selecting the initial list of H/PH constituents?

*The Subcommittee reviewed and edited the list of criteria to be recommended to TPSAC, as understood by CTP. The changes made by the Subcommittee are included in **red italics**.*

CTP's Understanding of the Criteria to be Recommended to TPSAC

- Identified by International Agency for Research on Cancer (IARC) as:
 - Sufficient evidence in humans or sufficient evidence in animals and strong mechanistic data in humans (Group 1)
 - Limited evidence in humans and sufficient evidence in animals (Group 2A)
 - Limited evidence in humans and less than sufficient evidence in animals (Group 2 B)
- Identified by Environmental Protection Agency (EPA) or the Agency for Toxic Substances and Disease Registry (ATSDR) as a respiratory or cardiac toxicant
- Identified by the California EPA as a reproductive or developmental toxicant
- One smokeless constituent included because it is banned in food
- Evidence for potential abuse liability
- Some constituents added on the basis of several published peer-reviewed studies suggesting cardiac or respiratory toxicity
- Evidence for potential abuse liability
 - ***Evidence of CNS activity***
 - ***Animal discrimination***
 - ***Conditioned Place Preference (CPP)***
 - ***Animal self-administration***
 - ***Human self-administration***
 - ***Drug “liking” Study***
 - ***Withdrawal (physical dependence)***
- Some constituents added on the basis of several published peer-reviewed studies suggesting cardiac or respiratory toxicity, ***or addiction***

2. What H/PH constituents do you recommend TPSAC include on the initial list of H/PH constituents in tobacco products or tobacco smoke?

*The Subcommittee reviewed and edited the list that was produced during the June 8-9, 2010 meeting of the Tobacco Product Constituents Subcommittee. The revised list is included as an attachment to these minutes, and the Subcommittee's edits are included in **red italics**.*

3. Which smoking regimen or regimens does the Subcommittee recommend to TPSAC be used to measure H/PH constituents?

After discussion, the Subcommittee agreed that no method will truly represent the consumer exposure, and recommended two smoking regimens:

ISO – for historical perspective

Health Canada Intensive – to determine performance of the product

4. What analytical parameters (e.g., accuracy, reproducibility, repeatability, throughput) do you recommend to TPSAC as those FDA should consider in comparing methods?

The Subcommittee recommended that the following analytical parameters should be considered:

- *Accuracy, reproducibility (between labs), repeatability (within a lab), and sensitivity (limit of detection, particularly relevant to level of constituent) of methods*
 - *Use of standard reference materials -> basis for comparison*
 - *Determine range of reproducibility and repeatability (both within and across laboratories)*
 - *Obtain temporary baseline until more data is available*
- *Reproducibility and repeatability may be relatively more important than accuracy (in absence of a reference material)*
- *Confirmation of accuracy and method by external lab*
- *Ability to get information on multiple analytes from single method (throughput – economic consideration)*
- *Flexibility over time – processes will evolve*

5. What considerations do you recommend to TPSAC as those FDA should take into account when developing a sampling plan for tobacco products? For example:

- *How should the number of replicates be determined?*
- *How often should tobacco products be tested?*
- *Should the products be analyzed immediately after they are manufactured or stored under certain environmental conditions to simulate shelf time?*
- *Are there other important considerations regarding tobacco product collection and storage?*

The Subcommittee made the following recommendations, to be considered by the TPSAC:

- *Need to gain understanding of the products as experienced by the consumer (sampling at the retail level)*
 - *Will include variation due to temporal, climatic, regional factors*
- *At least annual sampling (perhaps more often for smokeless)*
- *As information is accumulated, may prove testable with simpler sampling scheme (e.g. from point of manufacture)*
- *Information already available from other countries, tobacco industry, NCI smokeless TOBPRAC study in progress (should be considered before final decision)*

6. Are there other important scientific information / parameters that the Subcommittee recommends to TPSAC as those FDA should consider in measuring H/PH constituent levels?

The discussion of this question had been started at the June meeting, and so the Subcommittee reviewed their initial thoughts and made the following recommendations:

Normalization (from June meeting)

Data should be collected in a way that allows normalization of reported constituent quantities as follows:

- ***Cigarettes:*** *per nicotine, per stick, per gram total particulate material (allows comparison across products), per gram of tar*
- ***Smokeless Tobacco:*** *per nicotine, per gram of dry weight, per portion, per tin/container of product*
- *Extraction procedures – same protocol may produce different results, dependent on tobacco matrix*
- *Measure pH over time (both in smoke and smokeless) – relates to addiction potential (at this point in time, no specific method has been recommended for smoke)*
- *Surveillance of constituents over time*
- *Information on things that may influence testing*
 - *Ventilation, porosity, pH, blend, weight/stick or pouch, puff number, cut width, moisture, filter type, additives*
 - *Characteristics of cigarettes should be integrated with smoke yield*

The meeting adjourned at 4:00 p.m. on July 7, 2010.

Please see the *verbatim* transcript for details of the discussion.

If you have difficulty accessing this document, please call 1-877-287-1373 for assistance.

The RED text indicates changes made by the Subcommittee at the July 7, 2010 meeting.

Draft Initial List of Harmful/Potentially Harmful Constituents in Tobacco Smoke or Smokeless Tobacco Products							
		<i>Association with Tobacco Smoke or Smokeless Tobacco Product-Related Disease</i>					
	Constituent Present in Tobacco Smoke (S) and/or Smokeless Tobacco Products (ST)	Carcinogen	Respiratory Toxicant	Cardiovascular Toxicant	Reproductive or Developmental Toxicant	Addictive	Analytical Methods Available
Acetaldehyde	S, ST	IARC 2B, NTP - RAHC	NLM (HSDB), Wynder et al. 1965, Hoffmann et al. 1997	Egle and Hudgins, 1974	O'Shea and Kaufman 1981, Sreenathan et al. 1982	NLM (HSDB), Belluzzi et al., 2005, Talhout et al., 2007 Potential	YES
Acetamide	S	IARC 2B					YES
Acetone	S		ATSDR (Toxicological Profiles), EPA (IRIS)				YES
Acrolein	S		NLM (HSDB), Wynder et al. 1965, Hoffmann et al. 1997	Egle and Hudgins 1974	Slott and Hales 1985		YES
Acrylamide	S	IARC 2A, EPA-PrHC					YES
Acrylonitrile	S	IARC 2B, NTP - RAHC	ATSDR (Toxicological Profiles)				YES

Aflatoxin B-1	ST	IARC 1			Vesely et al. 1983, Keeler and Tu 1983, Gabor et al. 1973, Kihara et al. 2000		YES
4-aminobiphenyl	S	IARC 1, NTP-KHC					YES
1-aminonaphthalene	S	CDC: NIOSH (2010) potential occupational carcinogen					YES
2-aminonaphthalene	S	IARC 1, NTP-KHC					YES
Ammonia	S		ATSDR, Hoffmann and Hoffmann 2001			Further study needed	YES
Ammonium salts ion	ST		Sittig 1985		Shepard 1986	(tbd)	YES
Anabasine	ST	Hoffmann and Hoffmann 1997			Strudel and Gateau 1977	Hoffmann et al. 1997, Dani et al. 2009 (tbd) Potential	YES
Anatabine	ST	Hoffmann and Hoffmann 1997 Not a carcinogen				Hoffmann et al. 1997, Dani et al. 2009 (tbd) Further study needed	YES
o-Anisidine	S	IARC 2B	OSHA 2010				YES
Arsenic	S, ST	IARC 1, NTP-KHC		ATSDR (Toxicological Profiles)	Golub et al. 1998, CA EPA		YES
A- α -C	S	IARC 2B					YES
Benz[a]anthracene	S, ST	IARC 2B, EPA-PrHC		ATSDR (Toxicological Profiles)			YES

Benz[j]aceanthrylene	S	IARC 2B, Miller et al. 1990					YES
Benzene	S	IARC 1, NTP-KHC		ATSDR (Toxicological Profiles)	Kuna and Kapp 1981, CA EPA		YES
Benzo[b]fluoroanthene	S, ST	IARC 2B, EPA-PoHC		ATSDR (Toxicological Profiles)			YES
Benzo[k]fluoroanthene	S, ST	IARC 2B, EPA-PrHC		ATSDR (Toxicological Profiles)			YES
Benzo(b)furan	S	IARC 2B					YES
Benzo[a]pyrene	S,ST	IARC 1, NTP-RAHC		Harris 1996	Shepard 1983		YES
Benzo[c]phenanthrene	S	IARC 2B, Levin et al. 1986					YES
Beryllium	S, ST	IARC 1, EPA-PrHC			Prakash et al. 1991		YES
1,3-Butadiene	S	IARC 2A, NTP-KHC	NLM (HSDB)	Hoffmann et al. 1997	CA EPA		YES
Butyraldehyde	S		Hoffmann et al. 1997	Freeman et al. 2005, Guth 1996, Rumley et al. 2004			YES
Cadmium	S, ST	IARC 1, NTP-KHC	ATSDR (Toxicological Profiles)	Hoffmann et al. 1997, Navas-Acien et al. 2004	CA EPA		YES
Caffeic acid	S	IARC 2B					YES
Carbon monoxide	S			DHHS 1983	CA EPA, IPCS 1999		YES
Catechol	S	IARC 2B			Bingham et al. 2001		YES
Chlorinated dioxins/furans	S	NTP-KHC			Couture et al. 1990, CA EPA		YES

Chromium	S, ST	IARC 1, NTP-KHC	ATSDR (Toxicological Profiles)		ATSDR (Toxicological Profiles), CA EPA		YES
Chrysene	S, ST	IARC 2B, EPA-PrHC		ATSDR (Toxicological Profiles)	Hoffman and Gay 1981		YES
Cobalt	S	IARC 2B		ATSDR (Toxicological Profiles)	Ridgway and Karnofsky 1952, Adhikari 1967, Kury and Crosby 1968		YES
Coumarin*	ST				WHO 1981		YES
Cresols	S	EPA: o-cresol, m cresol, p-cresol -PoHC	Wynder et al. 1965				YES
Crotonaldehyde	S,ST	EPA - PoHC	Fernandez and Solomons 1962, Wynder et al. 1965	Freeman et al. 2005, Rumley et al. 2004			YES
Cyclopenta[c,d]pyrene	S	IARC 2A					YES
Dibenzo[a,h]acridine	S	IARC 2B, NTP-RAHC		ATSDR (Toxicological Profiles)			YES
Dibenzo[a,j]acridine	S	IARC 2B, NTP-RAHC					YES
Dibenzo[a,h]anthracene	S, ST	IARC 2A, EPA-PrHC, NTP - RAHC			Wolfe and Bryan 1939		YES
Dibenzo[c,g]carbazole	S	IARC 2B, NTP-RAHC					YES
Dibenzo[a,e]pyrene	S	IARC 2B, NTP-RAHC					YES
Dibenzo[a,h]pyrene	S	IARC 2B, NTP-RAHC					YES
Dibenzo[a,i]pyrene	S	IARC 2B, NTP-	NLM (HSDB)				YES

		RAHC					
Dibenzo[a,l]pyrene	S	IARC 2A, NTP-RAHC					YES
2,6-Dimethylaniline	S	IARC 2B					YES
Ethyl Carbamate (urethane)	S, ST	IARC 2B, NTP-RAHC			Nomura et al. 1996, Shepard 1986, CA EPA		YES
Ethylbenzene	S	IARC 2B			Tatrai et al. 1982, CDC: NIOSH 1981		YES
Ethylene oxide	S	IARC 1, NTP-KHC	NTP 1987, Rom 1992		Weller et al. 1999, CA EPA		YES
Eugenol	S, ST (respiratory toxicant)		NLM (HSDB), Clark 1988, LaVoie et al. 1986			(tbd)	YES
Formaldehyde	S, ST	IARC 1, NTP-RAHC	Hoffmann et al. 1997, Wynder et al. 1965	Egle and Hudgins 1974			YES
Furan	S	IARC 2B, NTP-RAHC					YES
Glu-P-1	S	IARC 2B					YES
Glu-P-2	S	IARC 2B					YES
Hydrazine	S	IARC 2B, EPA-PrHC, NTP-RAHC	Sullivan and Krieger 1992		ACGIH 2001		YES
Hydrogen cyanide	S		Hoffmann et al. 1997, Hoffmann and Hoffmann 2001, ATSDR (Toxicological Profiles)	Hoffmann et al. 1997, ATSDR (Toxicological Profiles)			YES
Hydroquinone	S	Gopalakrishna et al. 1994: possible tumor promoter					YES
Indeno[1,2,3-cd]pyrene	S, ST	IARC 2B, EPA-PrHC, NTP-					YES

		RAHC					
IQ	S	IARC 2A, NTP-RAHC					YES
Isoprene	S	IARC 2B, NTP-RAHC	Melnick et al. 1996				YES
Lead	S, ST	IARC 2A, NTP-RAHC		ATSDR (Toxicological Profiles)	ATSDR (Toxicological Profiles), CA EPA		YES
MeA- α -C	S	IARC 2B					YES
Mercury	ST	IARC 2B			IPCS, CA EPA		YES
Methyl ethyl ketone (MEK)	S		ATSDR (Toxicological Profiles)				YES
5-Methylchrysene	S	IARC 2B, NTP-RAHC					YES
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	S, ST	IARC 1, NTP-RAHC, Hoffmann and Hoffmann 1997					YES
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	S, ST	Rivenson et al. 1988, Hecht 1998					YES
Myosmine	ST					Hoffmann et al. 1997, Dani et al. 2009 (tbd) Further study needed	YES
Naphthalene	S, ST	IARC 2B, NTP-RAHC	ATSDR (Toxicological Profiles)		EPA		YES
Nickel	S, ST	IARC 1, NTP-RAHC	ATSDR (Toxicological Profiles)		ATSDR (Toxicological Profiles)		YES
Nicotine	S, ST			Hoffmann et al. 1997	Dempsey and Benowitz 2001, CA EPA	DHHS 1988 Confirmed	YES

Nitrate	S, ST	Hoffmann and Hoffmann 1997 <i>*primary indicator of toxicity of the tobacco</i>	Hoffmann and Hoffmann 1997				YES
Nitric oxide/nitrogen oxides	S		Hoffmann and Hoffmann 2001	Benowitz 2003	Tabacova 1985		YES
Nitrite	ST	Hecht 1998 <i>*primary indicator of toxicity of the tobacco</i>					YES
Nitrobenzene	S	IARC 2B, NTP-RAHC, EPA-LC	NLM (HSDB)		CA EPA		YES
Nitromethane	S	IARC 2B, ACGIH 2008 - confirmed animal carcinogen	IPCS 1997		ACGIH 2001		YES
2-Nitropropane	S	IARC 2B, NTP-RAHC	Mackinson et al. 1981		Sheftel 2000		YES
N-nitrosoanabasine (NAB)	S, ST	IARC (2007): limited evidence of carcinogenicity in experimental animals; not classifiable in humans					YES
N-Nitrosodiethanolamine (NDELA)	S, ST	IARC 2B, NTP-RAHC					YES
N-Nitrosodiethylamine	S	IARC 2A, EPA-PrHC, NTP-RAHC					YES
N-nitrosodimethylamine (NDMA)	S, ST	IARC 2A, EPA-PrHC					YES

N-Nitrosoethylmethylaniline	S	IARC 2B, EPA-PrHC					YES
N-nitrosomorpholine (NMOR)	ST	IARC 2B, NTP-RAHC					YES
N-nitrosornicotine (NNN)	S, ST	IARC 1, NTP-RAHC, Hoffmann and Hoffmann 1997					YES
N-Nitrosopiperidine (NPIP)	S, ST	IARC 2B, NTP-RAHC					YES
N-nitrosopyrrolidine (NPYR)	S, ST	IARC 2B, NTP-RAHC					YES
N-nitrososarcosine (NSAR)	ST	IARC 2B, NTP-RAHC					YES
Nornicotine	ST	Hoffmann and Hoffmann 1997				Hoffmann et al. 1997, Dani et al. 2009 (tbd) Potential	YES
Phenol	S	Tumor Promoter - ATSDR (Toxicological Profiles), Boutwell and Bosch 1959, Hoffmann and Hoffmann 2001	Wynder et al. 1965	ATSDR (Toxicological Profiles)	ATSDR (Toxicological Profiles)		YES
PhIP	S	IARC 2B, NTP-RAHC					YES
Polonium-210 (Radio-isotope)	S, ST	IARC 1, Wiggs et al. 1991					YES
Propionaldehyde	S		Wynder et al. 1965, Hoffmann et al. 1997	Egle and Hudgins 1974, Guth 1996			YES
Propylene oxide	S	IARC 2B, NTP-RAHC, EPA-PrHC	Bureau of Explosives 1981				YES

Pyridine	S		Perov 1973, Hoffmann and Hoffmann 2001				YES
Quinoline	S	EPA - LC					YES
Resorcinol	S		HDSB 2010, Dalhamn and Lagerstedt 1966				YES
Selenium	S, ST		ATSDR (Toxicological Profiles)				YES
Styrene	S	IARC 2B					YES
Tar	S	Wynder et al. 1953					YES
2-Toluidine	S	IARC 2A, NTP- RAHC		Patty 1963			YES
Toluene	S		ATSDR (Toxicological Profiles)		ATSDR (Toxicological Profiles), CA EPA		YES
Trp-P-1	S	IARC 2B					YES
Trp-P-2	S	IARC 2B					YES
Uranium-235	ST	IARC 1	Mackinson et al. 1981		Domingo 2001		YES
Uranium-238	ST	IARC 1	Mackinson et al. 1981		Domingo 2001		YES
Vinyl Acetate	S	IARC 2B	Sittig 1985		ECB 2005		YES
Vinyl Chloride	S	IARC 1, NTP- KHC					YES

The RED text indicates changes made by the Subcommittee at the July 7, 2010 meeting.							
(tbd) - to be discussed							
* - Banned as a food additive by the FDA							
The question of whether menthol should be included as a H/PH constituent was deferred, given that TPSAC is reviewing the effects of menthol cigarettes on public health.							

Carcinogen Column: IARC Classification¹		
IARC 1	Sufficient evidence in humans or sufficient evidence in animals and strong mechanistic data in humans	Carcinogenic to humans
IARC 2A	Limited evidence in humans and sufficient evidence in animals	Probably carcinogenic to humans
IARC 2B	Limited evidence in humans and less than sufficient evidence in animals	Possibly carcinogenic to humans

NTP Carcinogen Classification Abbreviations²	
KHC	Known human carcinogen
RAHC	Reasonably anticipated to be a human carcinogen

EPA Carcinogen Classification Abbreviation³	
PrHC	Probable human carcinogen
PoHC	Possible human carcinogen
LC	Likely to be carcinogenic